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Microvascular Reactions to Postural Changes in Patients with Sickle Cell Anaemia

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Normal microcirculation of the lower extremity is characterized by the venoarteriolar vasoconstriction reflex and the disappearance of vasomotion in the dependent position. Patients with sickle cell disease are prone to develop ischemic leg ulcers at an early age. Dysfunction of the microcirculation might promote the development of leg ulcers in patients with sickle cell disease. Using laser Doppler equipment we have studied the changes of blood flux in the skin overlying the medial malleolus after leg lowering. Contrary to the normal physiological situation seen in our control persons, the venoarteriolar reflex was abolished and vasomotion preserved in the dependent position of the leg in both patients. We conclude that this may represent an adaptation to the dependent position in sickle cell disease. ***Key words: leg ulceration; skin blood flow; laser Doppler flowmetry.***

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Ischemic leg ulcers are the most frequent dermatological complication of sickle cell disease (1). Although the exact pathogenesis of leg ulcers has not been elucidated, it has been postulated that plugging of small cutaneous vessels by stiff pathologic red cells causes tissue ischemia, infarction and finally ulceration (1–3). The fact that ulcers are localized almost exclusively in the dependent areas suggests that gravitational factors play a role in the development of ulcer.

In healthy individuals gravitational stress caused by a change of the body position from horizontal to dependent triggers vasoconstriction of vessels in microcirculation (the venoarteriolar reflex – VAR) (4). Moreover, vasomotion that promotes blood passage through capillaries is suppressed in the dependent position (5). Due to both mechanisms skin perfusion is impaired in the upright posture. It is thus conceivable that in patients with sickle cell anaemia the postural impairment of blood flow can further hinder the passage of blood cells through capillaries and promote the development of skin ulceration. We therefore investigated whether VAR is elicited, and vasomotion suppressed, due to gravitational stress in patients with sickle cell disease.

PATIENTS AND METHODS

Two women, citizens of Trinidad, age 22 and 19, with previously diagnosed sickle cell disease entered the study after they had given their informed consent. Patient 1 had a long history of leg ulceration, and since January she has been treated topically with flamazine. Patient 2 had never suffered from leg ulcers. The patients were not taking any long-term medications other than zinc sulphate (90 mg, daily) and had never received a blood transfusion.

The control recordings were obtained from 4 healthy women (16, 17, 24, 26 years old).

The theory of laser Doppler fluxmetry and the rationale for its use to evaluate the venoarteriolar reflex and vasomotion have been described in detail elsewhere (6, 7). We used a MBF3/D laser Doppler blood flow monitor (Moor Instruments, U.K.) and an integrated probe that measures blood flux from about 12 mm^2 of skin surface. Flux (product of average speed and concentration of moving red blood cells in the tissue sample volume) is measured in arbitrary perfusion units (range 0–1000). The measurements took place in the middle of the day, at a constant room temperature of 21°C, approximately 3 h after a moderate breakfast. The examinations were preceded by a 15-min acclimatisation period in the supine position. An unheated probe in a standard round plastic holder was placed 10 cm above the medial malleolus and held in this position with double-sided adhesive rings (Beiersdorf, Germany). Skin blood flux traces were recorded initially while the subject remained in the supine position (5 min-"flux 1") and another 5 min following leg lowering 50 cm below the heart level ("flux 2"). Previous investigations showed that after this manoeuvre VAR is reproducibly and selectively activated (4, 5, 8), and it is known that the reflex from baroreceptors is not triggered in these conditions (4). The speed of the recording was set to obtain two determinations of flux per second (in total 600 determinations/5 min). The data were fed into a PC computer and analysed with the software "Moorsoft" and "FFT", manufactured and provided by Moor Instruments. Average values of blood flux from the horizontal and dependent leg positions were calculated and the VAR index, which is independent of the initial flux values, was expressed as follows:

$$\frac{\text{mean flux 1-mean flux 2}}{\text{mean flux 1}} \times 100\%$$

For evaluation of vasomotion, power spectra densities were obtained from data of "flux 1" and "flux 2" with a fast Fourier algorithm in "FFT", and the frequency and power of the dominant amplitude were determined.

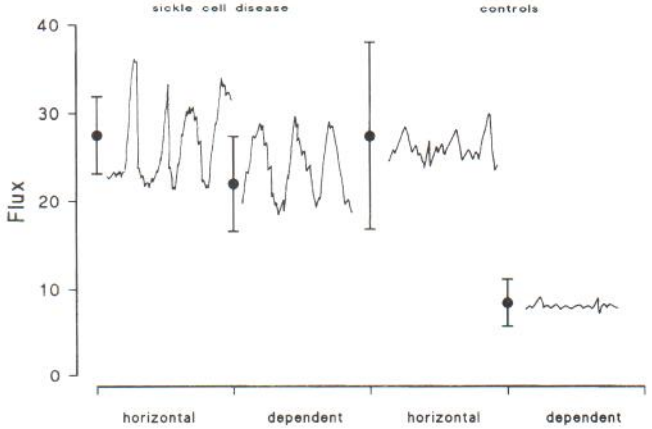

Fig. 1. Representative blood flux recordings from a patient with sickle cell disease and a healthy individual. *Bars* represent mean values of flux ±2SE for the patients and the controls, in the horizontal and dependent position, respectively.

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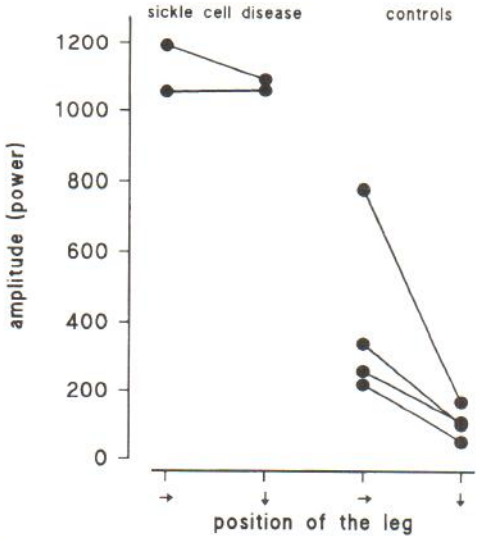

Fig. 2. Changes of the power of the dominant harmonic components of the vasomotion caused by leg lowering in patients with sickle cell anaemia and healthy individuals.

Results are presented as means ± standard error of the mean. A two-sided *t*-test was used as a test of significance.

RESULTS

Representative blood flux recordings from patient 1 and a control person are presented in Fig. 1. In the supine position the mean baseline blood flux (mean flux 1) over the medial malleolus did not differ between the patients with sickle cell disease (27.5 ± 2.2) and the controls (27.4 ± 5.3). The frequency of the dominant harmonic components of vasomotion was 0.17 ± 0.02 Hz in the patients and 0.12 ± 0.02 Hz in the controls (a non-significant difference). The mean power of the amplitude of the dominant harmonic components was, however, significantly higher than in the controls (1124 ± 28 *vs.* 400.8 ± 128.8, p = 0.02).

After leg lowering a statistically significant ($p < 0.001$) decrease of blood flux was recorded only in the control group; in the patients no change of blood flux took place (Fig. 1). The VAR index equalled 68.7 ± 1.8% in the controls, and 20.3 ± 3.4% in the patients. Also the mean power of dominant harmonic components decreased in controls (to 106.2 ± 24.1, $p < 0.001$), but not in the two patients with sickle cell anaemia (1076 ± 16) (Fig. 2). Frequencies of the dominant harmonic components did not change after leg lowering in the two patients with sickle cell anaemia.

DISCUSSION

Our studies showed that gravitational stress elicited a different microvascular response in patients with sickle cell disease than in healthy individuals: after leg lowering postural vasoconstriction due to VAR was virtually absent, and the vasomotion was preserved.

We evaluated vasomotion with the fast Fourier transformation. In this method a complex waveform pattern is decomposed into a series of harmonic sine and cosine components (power spectrum). After transformation of the power spectrum to the power spectrum density, the power of each discrete component can be measured. In our patients the dominant harmonic component of vasomotion had a slightly higher frequency than in the controls, and nearly three times the power of the amplitudes. Moreover, after leg lowering the power of dominant amplitudes decreased significantly in the controls, but did not change in the patients. These findings are in accordance with the data of Rodgers et al. (7), who showed that patients with sickle cell disease demonstrated vigorous flux motion in skin microcirculation at the mean frequency 0.12 Hz. The mechanism of the enhancement of vasomotion in sickle cell disease is not known. In normal conditions variability of flow in the subpapillary plexus and in the capillaries, detected with laser Doppler technique, is composed of rhythmic oscillations of different frequencies (0.025–0.35 Hz); the low-frequency components are generated in the largest arterioles, whereas the high-frequency oscillations originate in the small, precapillary vessels (9, 10). It has been speculated that in sickle cell disease vasomotion of the precapillary arterioles is synchronised, and thus periodic oscillations of flow become less chaotic and readily detectable (3, 7). Vasomotion in sickle cell disease is probably triggered by the sickle cells themselves, since periodic oscillations of blood flux were reported to disappear after blood transfusion (7).

Vasomotion increases blood fluidity, total capillary flow, and facilitates detachment of cells from the vessel wall (11). Therefore, in patients with sickle cell disease vasomotion probably constitutes an important mechanism enabling passage of stiff sickle cells through microvasculature (3). In view of the beneficial role of vasomotion, its preservation after lowering of the leg, observed by us, reflects an adaptation mechanism counteracting skin hypoperfusion and ischemia elicited by gravitational stress in patients with sickle cell disease.

VAR was abolished in our patients with sickle cell disease. Under physiological conditions VAR causes tissue hypoperfusion, and under these circumstances polymerization of pathologic haemoglobin S and transformation of the intracellular fluid into a viscoelastic gel would take place (12). Cells of increased stiffness could easily be trapped at the entrance of narrow capillaries and cause tissue infarction. Therefore, suppression of VAR in sickle cell disease seems to be an additional adaptation to gravitational stress. Suppression of VAR in sickle cell anaemia resembles in many ways the situation described in patients with occlusive arterial disease in the legs. Upon gravitational stress in the ischemic areas VAR is abolished and blood flow actually increases due to redistribution of flow from healthy places to the sites of ischemia (an "inverse steal") (13) and to capillary recruitment (14).

In healthy men VAR elicited by gravitational stress is a major mechanism preventing oedema formation in the upright posture. Suppression of VAR causes leg oedema by elevation of capillary pressure and enhancement of transcapillary fluid filtration (15, 16). It is interesting that despite an almost total suppression of VAR in sickle cell disease we did not see leg oedema in our patients. To our knowledge, association between sickle cell disease and leg oedema has not been reported. One explanation may be that vigorous vasomotion plays a role in the removal of the excess of fluid from the skin. It has been suggested that

vasomotion affects capillary pressure and fluid balance (17), and Colantuoni et al. (18) showed that during anaesthesia vasomotion is abolished and oedema is induced.

In summary, we have shown that in sickle cell disease postural vasoconstriction is abolished and vasomotion preserved after gravitational stress. We postulate that these phenomena represent adaptational modifications preventing leg ulcer development.

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